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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/966,724	10/01/2001	Kenneth W. Kinzler	01107.00193	3707

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/966,724	KINZLER ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,28,56,62 and 63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,28,56,62,63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/23/06,2/24/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/24/06 has been entered.

Claims 27, 28, 56 and 62-63 are pending.

Applicant's traversal and the addition of claims 62 and 63 in paper filed on 2/24/06 is acknowledged and considered.

The response to the non-complaint letter filed on 4/5/06 is acknowledged.

The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be to directed to Brian Whiteman, Art Unit 1635.

Priority

The status (abandoned, pending, issued as US Patent) of the parent applications listed on page 1 of the instant specification needs updated.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27, 28, 56, 62 and 63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 27, 28, 56, 62, and 63, as best understood, are readable on a genus of antisense oligonucleotides which are complementary to human MDM2 mRNA and which inhibit transcription or translation of a human MDM2 gene, wherein the genus of oligonucleotides is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates a genus of antisense oligonucleotides, which bind to the hMDM2 gene or mRNA and prevent transcription or translation (page 10). The term "mRNA" indicates that the term reads on pre-mRNA (mRNA with introns) or processed mRNA (mRNA without introns or mature mRNA). The skilled artisan understands that pre-mRNA is subject to a number of maturation processes before the mature mRNA is translocated into the cytoplasm and transcribed. For example, the introns are cut out of the pre-mRNA and the 5' end of the mRNA is capped. The specification discloses SEQ ID NO: 2 (Figure 1), which is the cDNA for human MDM2. The instant specification does not disclose a nucleotide sequence comprising the human MDM2 gene. The prior art does not disclose the nucleotide sequence for the human

MDM2 gene. Branch teaches, "internal structures of target RNAs and their association with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules (page 45 cited on PTO892). Gerwitz et al. (PNAS, 93:3161-3163, 1996) teach that mRNA targeting is to some extent a hit or miss process, accounting for many experiments in which the addition of an ODN yields no effect on expression (page 3161)." Uhlmann et al. teach, "It is clear from most in vitro studies that antisense oligonucleotides act most efficiently when directed against the initial part of the 5' non-coding region near the cap structure and against the region around the translation start codon (page 576)." (Chemical Review, 90: 544-84, 1990, cited on a PTO1449). Uhlmann et al. further teach, "Every mRNA has an individual secondary and tertiary structure that has a crucial influence on the efficiency of the target sequences" (page 576). "Although mRNA secondary structures can be calculated the efficiency of antisense oligonucleotides as inhibitors of protein translation has to be determined experimentally in practice" (page 576). While, one skilled in the art can envision a sequence that binds to SEQ ID NO: 2, the skilled artisan would be unable to determine without further experimentation if the sequence had a function that was considered essential for the claimed genus of oligonucleotides. There is a variation among species of the claimed genus of oligonucleotides. For example, the genus embraces oligonucleotides that bind to introns and cap structures that are neither disclosed in the specification nor the prior art. In addition, the skilled artisan understands that human MDM2 with polymorphisms are embraced by the claimed genus that are not disclosed in the instant specification or prior art. Furthermore, the specification does not disclose how to make a sufficient number of species to represent the genus of claimed oligonucleotides. The specification does not make any oligonucleotides embraced by the

claimed genus. The only disclosure is part of paragraph in the specification contemplating an antisense oligonucleotide to hMDM2 gene or mRNA (bottom of page 10). In addition, the claimed genus embraces oligonucleotides that inhibit transcription by binding to human MDM2 mRNA; however, transcription has already occurred if the mRNA is produced. Thus, the specification does not disclose how to make oligonucleotides that bind to human MDM2 mRNA and inhibit transcription. The mere contemplation of the claimed genus in the specification is not sufficient to support the present claimed invention directed to a genus of antisense oligonucleotides. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of antisense oligonucleotides that must possess the biological properties as contemplated by applicants' disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CAFC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of antisense oligonucleotides that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in

the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicant's arguments filed 2/24/06 have been fully considered but they are not persuasive.

In response to applicant's argument that the present specification meets the written description requirement because it describes the recited antisense oligonucleotides by way of "relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties (see USPTO Written Description Guidelines, 66 Fed. Reg. 1099, 1106, (January 5, 2001), cited by approval in Enzo Biochem., Inc. v. Gen-Probe Incorporated, 296, F.3d 1316, 1325, 63 USPQ.2d 1609, 1613 (Fed. Cir. 2002), the argument is not found persuasive because the mere contemplation of the claimed genus of antisense oligonucleotides that inhibit transcription or translation of a human MDM2 gene is not sufficient to support the claimed genus. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). The art of record (James et al. Antiviral Chemistry and Chemotherapy, 2, 191-214, 1991 (cited on a PTO892 and Gerwitz et al. (supra) and Branch (cited on an PTO892), at the time of filing, indicates that it was not conventional in the art to produce antisense with the desired biological activity. "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004).

Therefore, the skilled artisan would have to further experiment with any oligonucleotide embraced by the genus to determine if the oligonucleotide meets the function of the claimed genus of oligonucleotides.

Applicant argues that the present specification teaches both the coding sequence of human MDM2 (including start and stop codon) and its 5' untranslated region (UTR) (Figure 1). In addition, at the time the application was filed (1992), those skilled in the art were well aware of the rules of complementary base pairing. Thus, with this knowledge the skilled artisan could envision every possible to antisense oligonucleotide, which is complementary to any portion of the disclosed sequence.

Applicant's argument is not found persuasive because the claims are broader than the coding sequence of hMDM2 and its 5' UTR (SEQ ID NO: 2). See the reasons set forth above in the rejection. The prior art, at the time of filing, has not established a strong correlation between structure and function of a genus of oligonucleotides and their function. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984). Thus, the skilled artisan could not envision every possible oligonucleotide because the hMDM2 gene was neither in the prior art nor the instant specification.

While it is acknowledged that in view of the rules of complementary base pairing, the skilled artisan could envision any oligonucleotide that is complementary to SEQ ID NO: 2 (Figure 1), as stated above, the claims are broader than SEQ ID NO: 2. Furthermore, the skilled artisan would be required to further experiment with the oligonucleotides to determine which oligonucleotide inhibits transcription or translation. Agrawal (TIBTECH, 14 376-387, 1996) teaches that the activity of an oligonucleotide in cell culture depends on many factors, including

chemical modifications, the cell culture model, and the sequence of the oligonucleotide (page 377). See, In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967) and Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1328, 56 USPQ2d 1481, 1487 (Fed. Cir. 2000).

In response to applicant's argument that several post-filing references demonstrate several MDM2 antisense oligonucleotides inhibit mRNA expression and the experiments described in the references used techniques that were well known in the art at the time of filing (1992), the argument is not found persuasive because the specification does not disclose how the skilled artisan could make and distinguish between antisense oligonucleotide with the desired biological activity (as set forth in the post-filing references) and antisense oligonucleotides without the desired biological activity. Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) ("it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it"). Thus, at the time of filing, the skilled artisan could not correlate from the disclosure in the specification to the species of antisense having the desired function embraced by the claimed genus of antisense oligonucleotides disclosed in the post-filing references.

Furthermore, the post-filing references are directed to antisense oligonucleotides against the coding sequences of hMDM2. As mentioned above, the claimed invention is broader than antisense oligonucleotides to the coding sequence of hMDM2.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764.

The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, SPE – Art Unit 1635, can be reached at (571) 272-4517.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman

BRIAN WHITEMAN
PATENT EXAMINER